



Select Route of Administration in Mammalian System of Interest & Barrier(s) to Absorption

Route of Administration

(Common Examples)

- Enteral
- Parenteral
- Inhalation
- Transdermal
- Ocular

Mammalian System (Common Examples)

- GI Tract
- Brain
- Respiratory
- Skin
- Eye

Absorption Barrier (Primary Barrier)

- Lumenal Tissue-Membrane
- Blood Brain Barrier Tissue-Membrane
- Nasal/Lung Tissue-Membrane
- Epidermal/Dermal Tissue-Membrane
- Ocular Tissue-Membrane

Select Assay/Parameters Based on Route/Mammal/Barrier & Generate *In vitro* Bioavailability Data For Test Samples From Primary Library

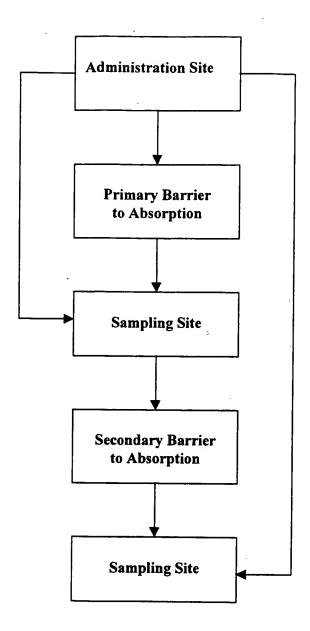
In vitro Bioavailability Assay/Data

Cell Culture/Tissue/Membrane Systems/SAR/QSAR

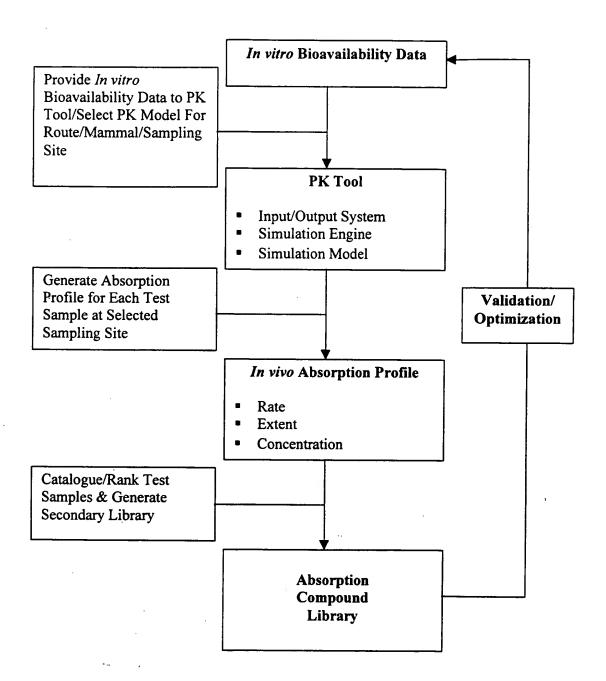
- Permeability
- (Transport Mechanism)*

Physiological Fluid/Solvent/Buffer Systems/SAR/QSAR

- Solubility
- (Dissolution Rate)*
- *optional



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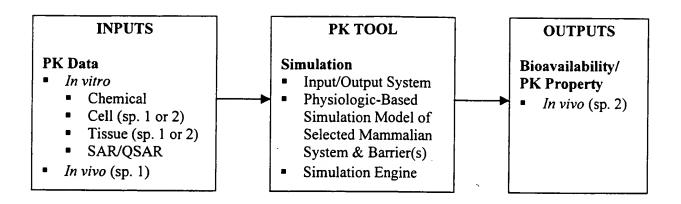
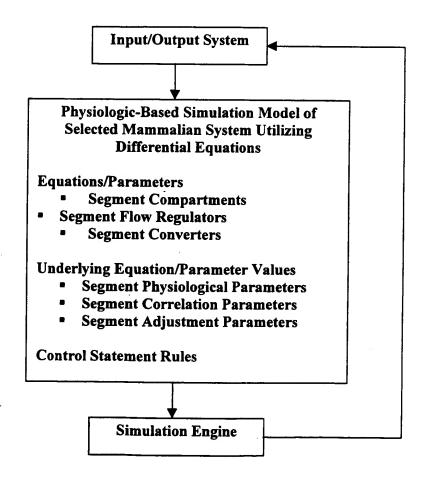


FIG. 5



Symbol

Name

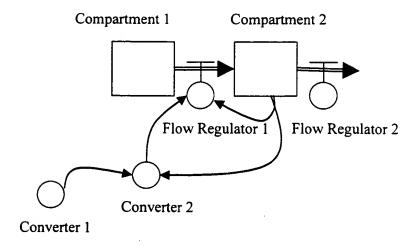


FIG. 7

Time-Dependent Function

	Compartment	Equation or value for amount of substance stored.
	Flow Regulator	Rate equation for amount of substance transferred.
\bigcirc	Converter	Equation or pre-defined value for (i) input into flow regulator; (ii) input into another converter; and/or (iii) storing value.
∼	Input Link	Directs input values.

FIG. 8

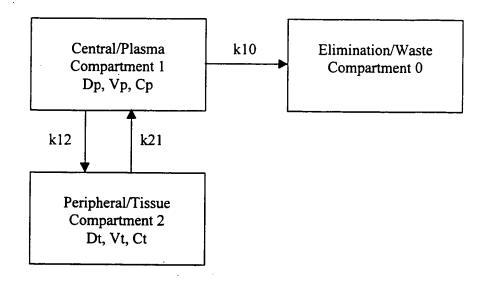
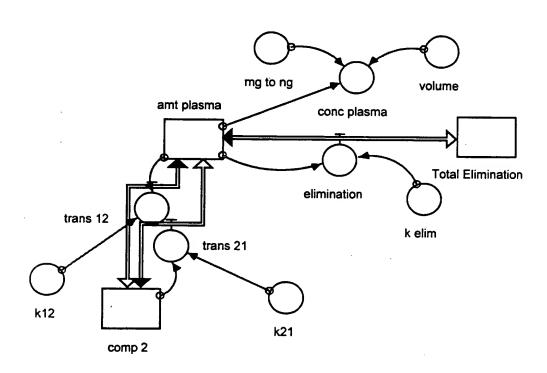
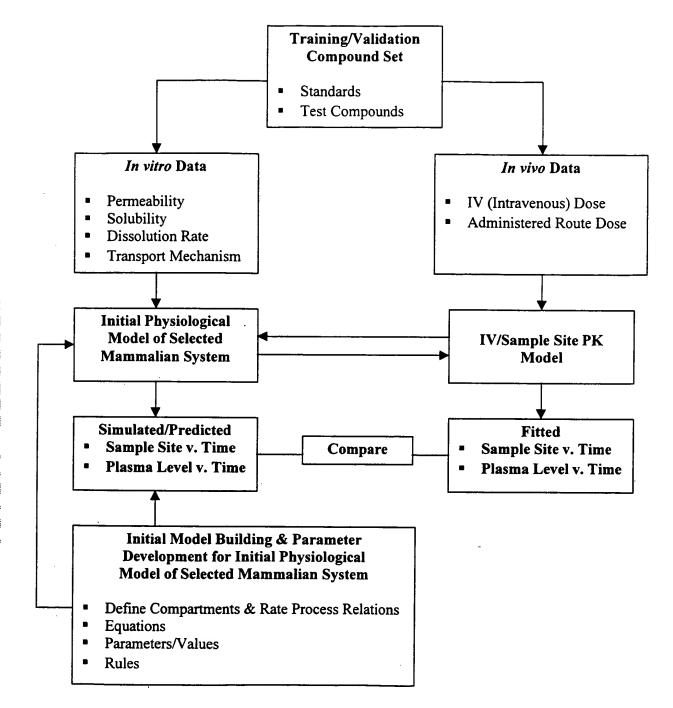
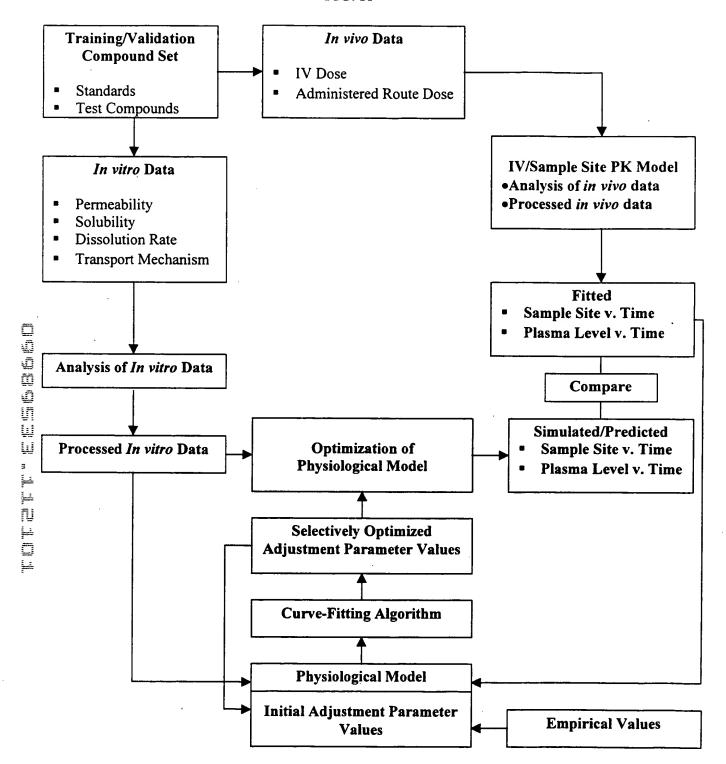
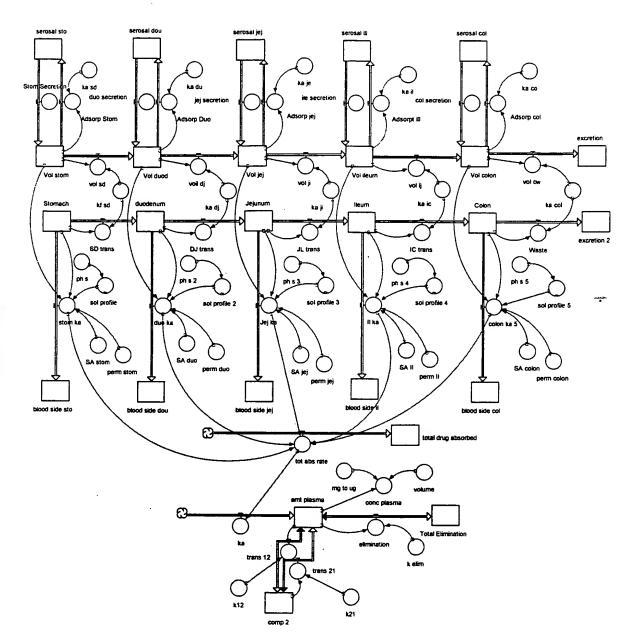


FIG. 9









Mass-Volume GI Tract Model

- GI Segment Compartments
 - Fluid Volume
 - Fluid Absorption
 - Insoluble Mass
 - Soluble Mass Absorption
- GI Segment Flow Regulators
 - Fluid Volume Absorption Rate
 - Fluid Volume Secretion Rate
 - Fluid Volume GI Transit Rate
 - Insoluble Mass GI Transit Rate
 - Soluble Mass Absorption Rate
- GI Segment Converters
 - Rate Constant
 - pH
 - Solubility
 - Surface Area
 - Permeability

FIG. 14

Mass-Volume GI Tract Model

- GI Segment Compartments & Flow Regulators
 - Fluid Volume
 - Fluid Volume Absorption Rate
 - Fluid Volume Secretion Rate
 - Fluid Volume GI Transit Rate
 - Fluid Volume Absorption
 - Fluid Volume Absorption Rate
 - Fluid Volume Secretion Rate
 - Insoluble Mass
 - Insoluble Mass GI Transit Rate
 - Soluble Mass Absorption Rate
 - Soluble Mass Absorption
 - Soluble Mass Absorption Rate

Mass-Volume GI Tract Model

- GI Segment Flow Regulators & Converters
 - Fluid Volume Absorption Rate
 - Fluid Volume Absorption Rate Constant
 - Fluid Volume Secretion Rate
 - Fluid Volume Secretion Rate Constant
 - Fluid Volume GI Transit Rate
 - Fluid Volume GI Transit Rate Constant
 - Insoluble Mass GI Transit Rate
 - Insoluble Mass GI Transit Rate Constant
 - Soluble Mass Absorption Rate
 - Fluid Volume
 - Insoluble Mass
 - Mass Solubility Profile
 - pH
 - Permeability
 - Surface Area

FIG. 16

Mass-Volume GI Tract Model

- GI Segment Converters
 - Rate Constant
 - pH
 - Solubility
 - Surface Area
 - Permeability

FIG. 17

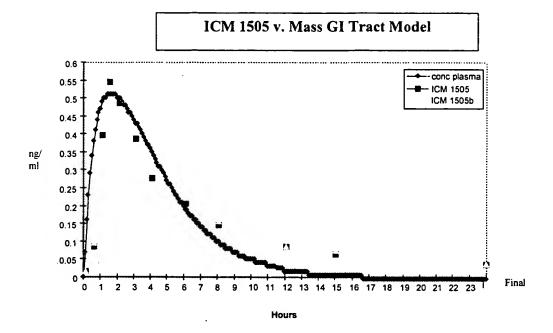
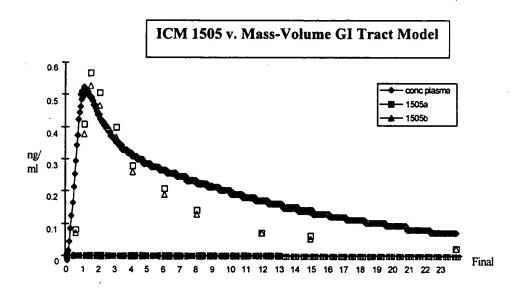
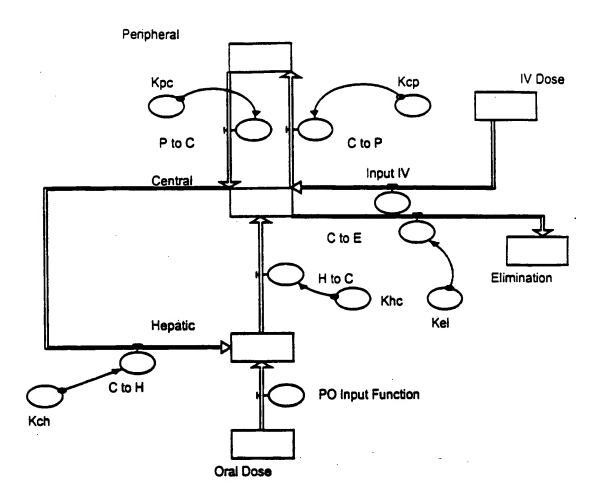
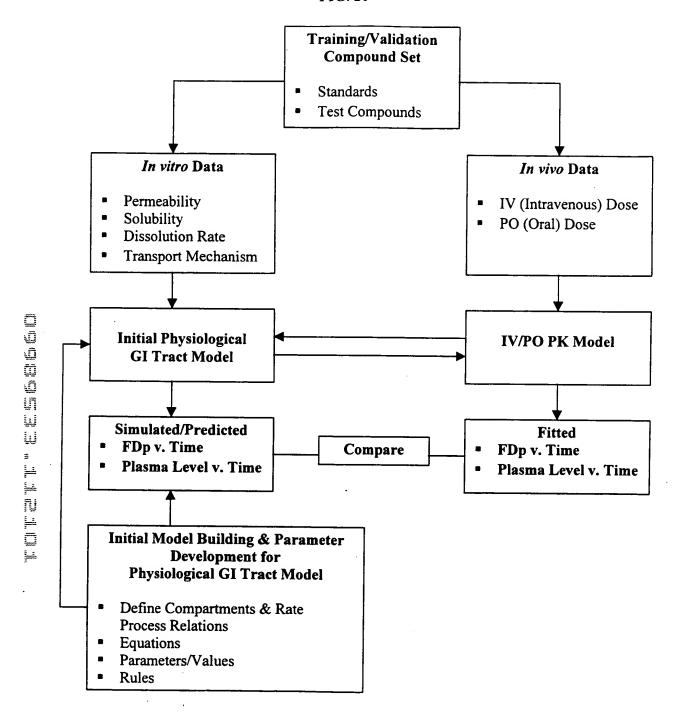


FIG. 18



Hours





Gastrointestinal Transit

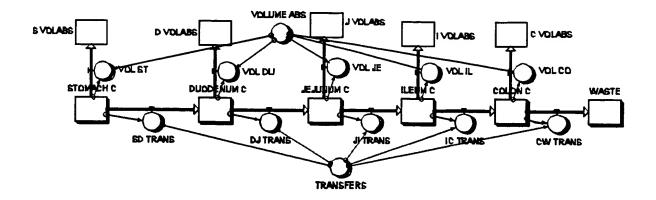


FIG. 22

pH Dependent Solubility and Dissolution

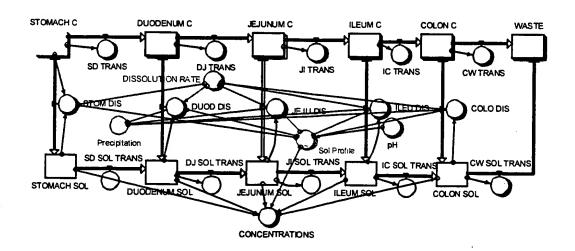


FIG. 23

Absorption

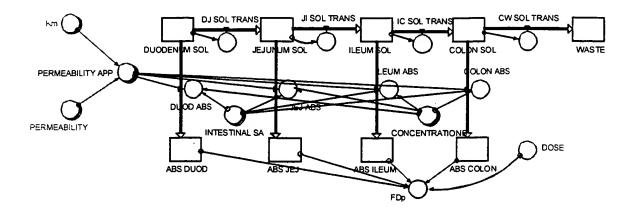


FIG. 24

GI Tract -Intestinal Model

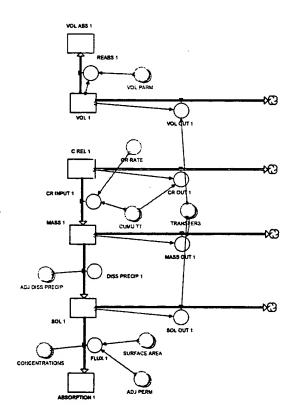


FIG. 25

GI Tract-Intestinal Model (without converters, ghosts or connectors)

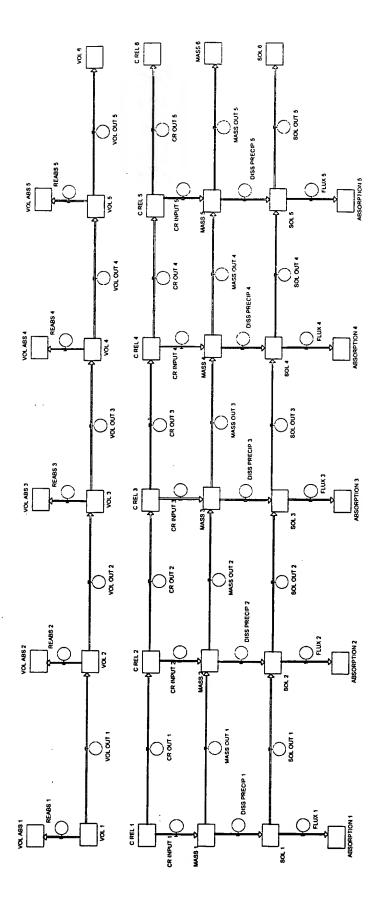
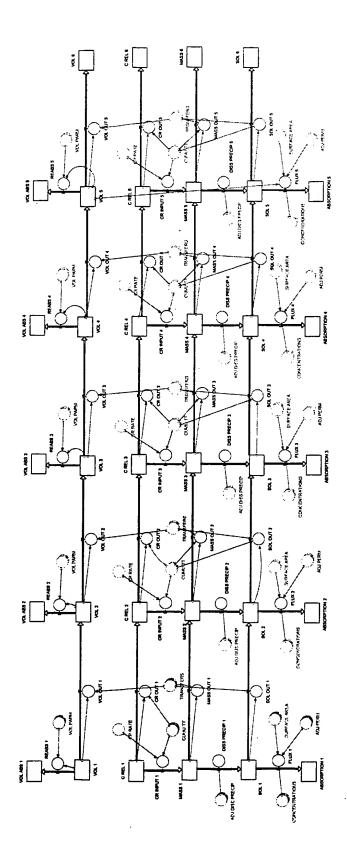
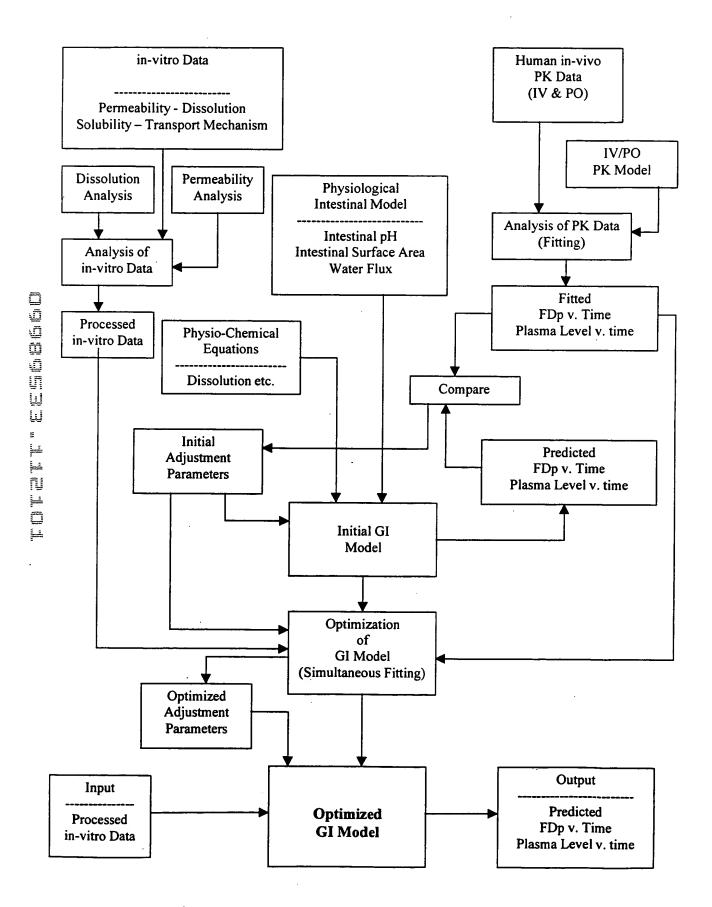


FIG. 26

GI Tract-Intestinal Model







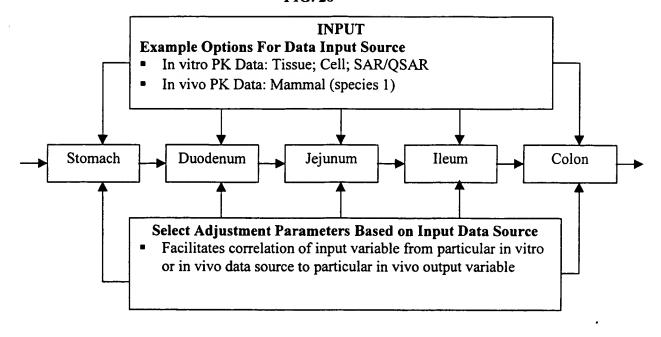
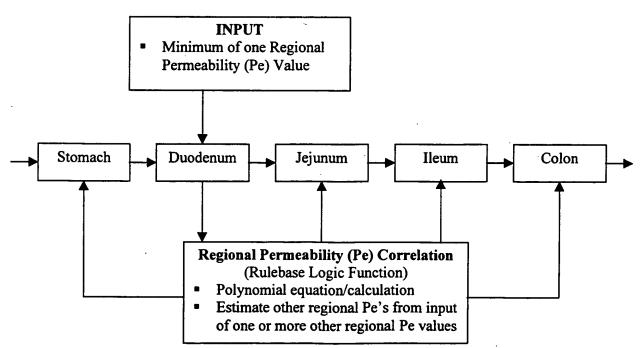


FIG. 29



Parameters

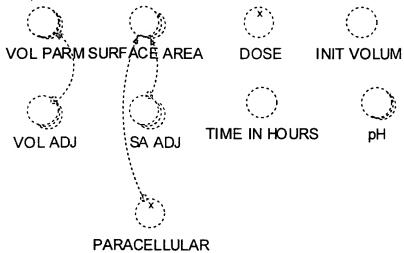


FIG. 31

Transit Time

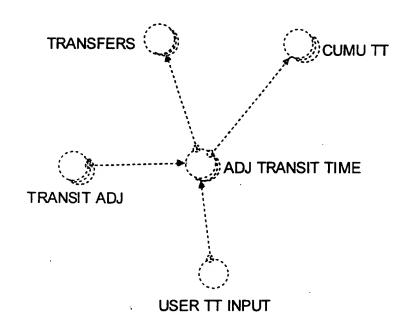


FIG. 32

Permeability Calculation

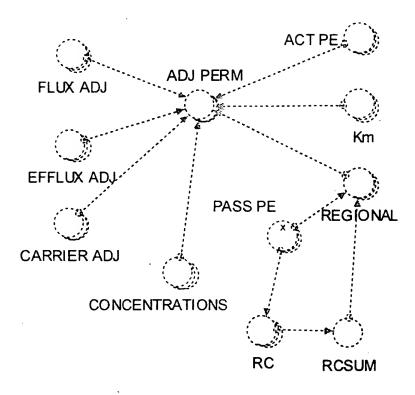
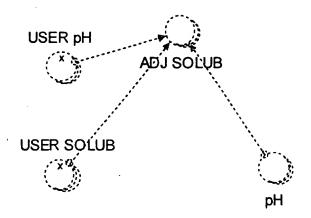


FIG. 33

Solubility Calculation



Control Release Calculation

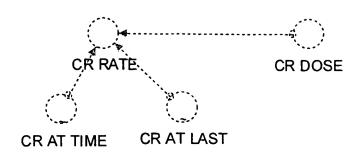
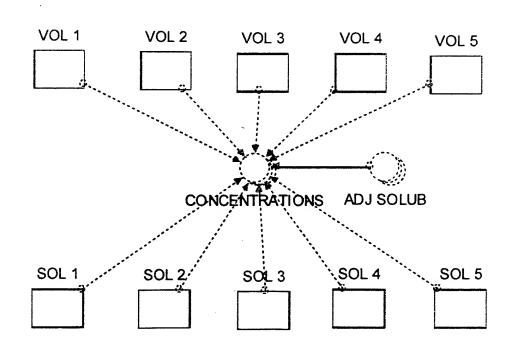


FIG. 35

Concentration Calculation



Dissolution Calculation

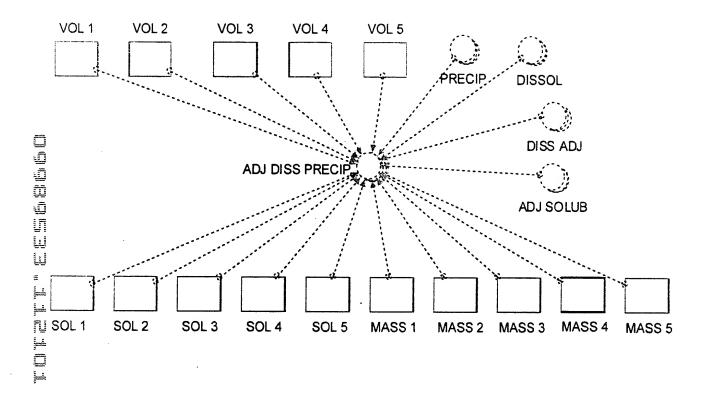
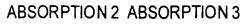
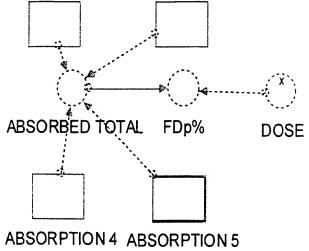


FIG. 37





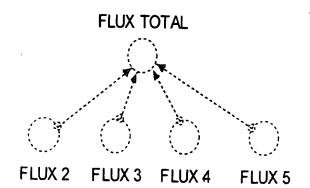


FIG. 39

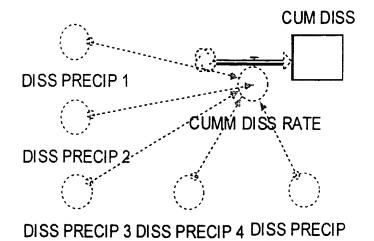
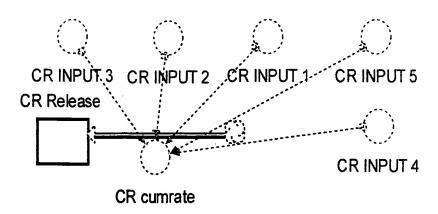


FIG. 40



Physiological GI Tract Model

Database

- GI Segment Compartments
 - Fluid Absorption
 - Fluid Volume
 - Insoluble Mass
 - Soluble Mass
 - Soluble Mass Absorption
 - Dosage Form Mass

GI Segment Flow Regulators

- Fluid Absorption Rate
- Fluid Volume Transit Rate
- Insoluble Mass Transit Rate
- Insoluble Mass Dissolution Rate
- Soluble Mass Transit Rate
- Soluble Mass Absorption Rate
- Dosage Form Disintegration/Release Rate

GI Segment Converters

- Fluid Volume Absorption Rate Constant
- GI Transit Rate Constant
- Adjusted Dissolution Rate Constant
- Dissolved Drug Concentration
- Adjusted Surface Area
- Adjusted Permeability

Rulebase

- GI Transit
- Dissolution
- Absorption
- Permeability Calculations
- Concentration Calculations
- Computational Error Corrections

Physiological GI Tract Model

- GI Segment Compartments & Flow Regulators
 - Fluid Absorption
 - Fluid Absorption Rate
 - Fluid Volume
 - Fluid Volume Absorption Rate
 - Fluid Volume Transit Rate
 - Insoluble Mass
 - Insoluble Mass Transit Rate
 - Insoluble Mass Dissolution Rate
 - Soluble Mass
 - Insoluble Mass Dissolution Rate
 - Soluble Mass Transit Rate
 - Soluble Mass Absorption Rate
 - Soluble Mass Absorption
 - Soluble Mass Absorption Rate

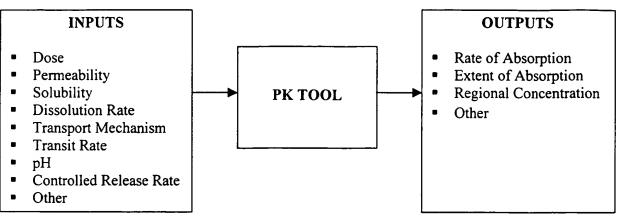
FIG. 43

Physiological GI Tract Model

- GI Segments Flow Regulators & Converters
 - Fluid Absorption Rate
 - Fluid Volume
 - Fluid Volume Absorption Rate Constant
 - Fluid Volume Transit Rate
 - Fluid Volume
 - Fluid Volume Transit Rate Constant
 - Insoluble Mass Transit Rate
 - Insoluble Mass
 - Insoluble Mass Transit Rate Constant
 - Insoluble Mass Dissolution Rate
 - Insoluble Mass
 - Dissolution Rate Constant
 - Soluble Mass Transit Rate
 - Soluble Mass
 - Soluble Mass Transit Rate Constant
 - Soluble Mass Absorption Rate (Flux)
 - Surface Area
 - Dissolved Mass Concentration
 - Permeability

Physiological GI Tract Model

- Converters
 - Permeability
 - Passive Absorption Adjustment Parameter
 - Efflux/Secretion Adjustment Parameter
 - Active Absorption Adjustment Parameter
 - Active or Carrier Mediated Absorptive Permeability
 - Km
 - Passive Permeability/Regional Correlation
 - Passive Permeability
 - Logic Function For Regional Correlation
 - Passive Permeability
 - Logic Function For Regional Correlation
 - Dissolved Mass Concentrations
 - Dissolved Mass Concentration
 - Fluid Volume
 - Solubility
 - pH
 - Solubility
 - Dissolution Rate Constant
 - Fluid Volume
 - Precipitation Rate Constant
 - Dissolution Rate Adjustment Parameter
 - Solubility
 - Insoluble Mass
 - Soluble Mass
 - Surface Area
 - Surface Area Adjustment Parameter
 - Transport Mechanism
 - Transit Rate
 - Transit Time Adjustment Parameter
 - User Adjusted Transit Time
 - Fluid Volume Absorption Rate Constant
 - Fluid Volume Adjustment Parameter



Select Model

Model Database

Physiological
GI Tract Model

Parameter Database

In vivo

Select Tissue Select SAR/QSAR Select Cell Select Mammal

Rate

FIG. 47 Simulation Engine Physiological GI Tract Model Start I/O Dose **Start Simulation** Permeability Stop Simulation Solubility Menu Rate of Absorption Dissolution Rate Extent of Absorption Transport Mechanism Concentration Transit Time Print Graph Print Table pН Quit Formulation Release

FIG. 48

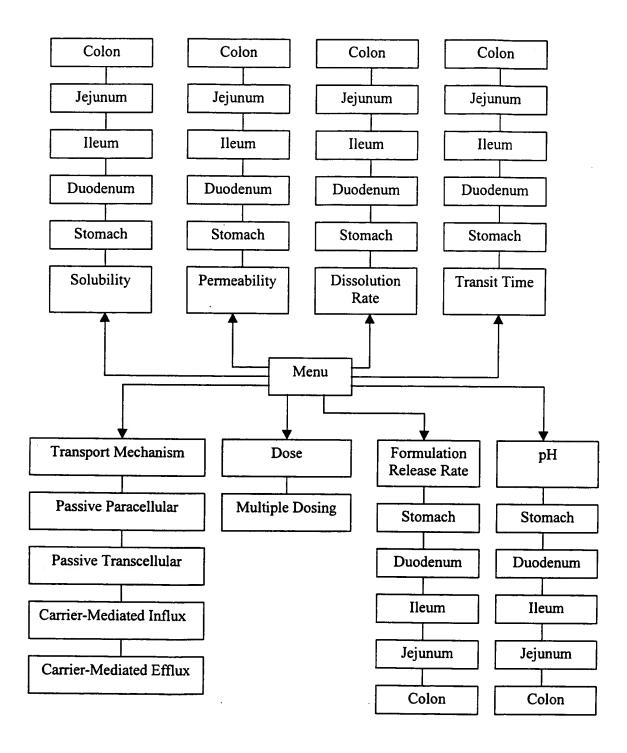


FIG. 49

Correlation of FDp Extent - GI Model and Pharmacokinetic data

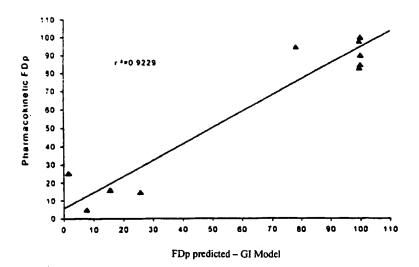


FIG. 50

Correlation of FDp rate of absorption - GI Model and Pharmacokinetic Data

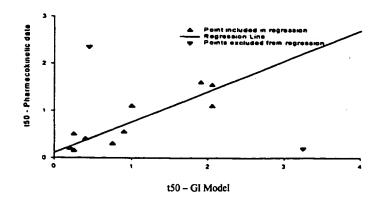
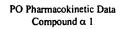


FIG. 51



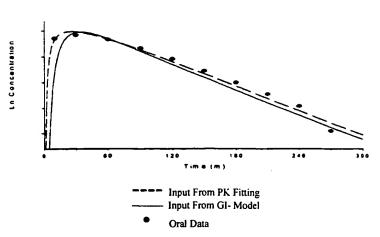


FIG. 52

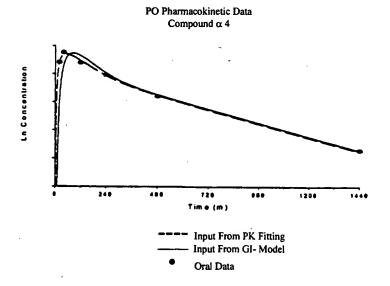
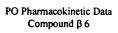
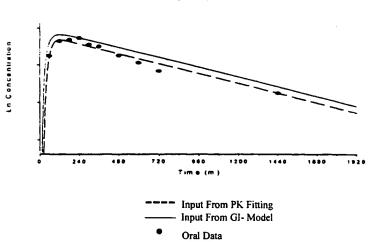


FIG. 53





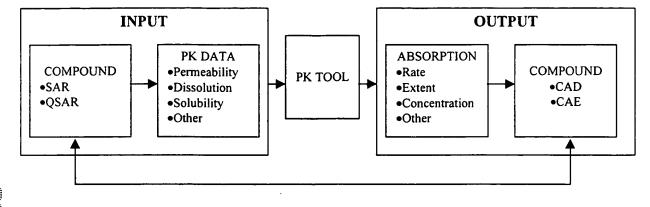


FIG. 55

